ACS Medicinal Chemistry Letters

Patent Highlight

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Imidazopyrazine Derivatives As Inhibitors of mTOR

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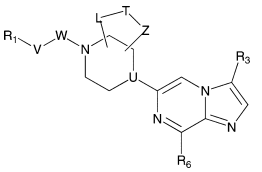
Title:	Imidazopyrazine Derivatives As Inhibitors of mTOR		
Patent/Patent Application Number:	WO 2013/016160 A1	**Publication date:**	January 31, 2013
Priority Application:	US 2011-449017P	**Priority date:**	July 26, 2011
Inventors:	Meng, Z.; Siddiqui, M. A.; Reddy, P. A. P.		
Assignee Company:	Merck Sharp & Dohme Corp., USA		
Disease Area:	Cancer	**Biological Target:**	Mammalian Target of Rapamycin (mTOR) Kinase

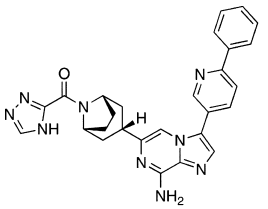
Summary: This application claims a series of imidazopyrazine analogues that may provide a treatment for cancer.

Important Compound Classes:

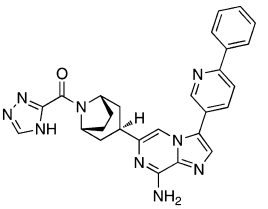


Definitions: U is N or CH

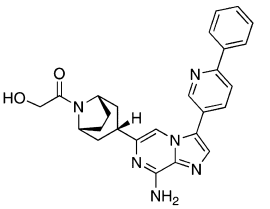
Key Structures:



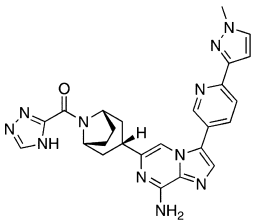
Compound 1



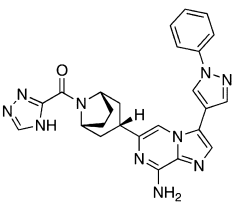
Compound 2



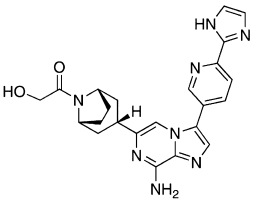
Compound 3



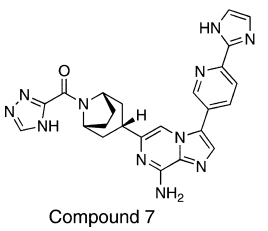
Compound 4



Compound 5



Compound 6



Compound 7

Recent Review Articles:

Malaguti, P.; Vari, S.; Cognetti, F.; Fabi, A. The mammalian target of rapamycin inhibitors in breast cancer: current evidence and future directions. *Anticancer Res.* **2013**, 33 (1), 21−28.

Johnson, S. C.; Rabinovitch, P. S.; Kaeberlein, M. mTOR is a key modulator of aging and age-related disease. *Nature* **2013**, *493* (7432), 338−345.

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Biological Assay: Compound inhibitory activity was evaluated using an HTRF mTOR enzyme assay. Inhibition of mTORC1 and mTORC2 was measured using an immunofluorescent cell-based assay. Inhibition of mTORC1 activity was measured by the reduction of the level of phosphorylated 4E-BP1Thr37/46 (p4E-BP1Thr37/46). Inhibition of mTORC2 activity was measured by the reduction of the level of phosphorylated AKTSer473 (pAKTSer473).

Pharmacological Data:

Compound	pAKTSer473 (IC_{50} nM)	p4E-BP1Thr37/46 (IC_{50} nM)
1	1-100	100-1000
2	-	-
3	100-1000	100-1000
4	1000-10000	1000-10000
5	1135	1863
6	1000-10000	>10000
7	>10000	>10000

Synthesis: Preparation of 7 compounds.

AUTHOR INFORMATION

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Notes

The authors declare no competing financial interest.